PATENT
Attorney Docket No.: 018512-006010US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

CREECH and JEGLA

Application No.: 09/855,828

Filed: May 14, 2001

For: CNG3B: A NOVEL CYCLIC NUCLEOTIDE-GATED CATION CHANNEL

Customer No.: 20350

Confirmation No. 9660

Examiner: Jon Lockard

Technology Center/Art Unit: 1647

DECLARATION UNDER 37 C.F.R. §1.132 OF DR. MCCORMACK

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ken McCormack, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I received a B.A. degree in Psychobiology from the University of California at Santa Cruz in 1985 and a Ph.D. in Neurobiology from the California Institute of Technology in 1991. I served as a postdoctoral fellow in the Department of Cellular and Molecular Biology at Yale University from 1991-92, the Max Planck Institute for Biophysical Chemistry and Experimental Medicine from 1992-95 and the Department of Genetics, Pathobiology and Physiology at the University of Wisconsin at Madison from 1995-97. I was the Group Leader for Molecular Biology at Arcaris/Deltagen Proteomics from 1997-2000 and a Principal Scientist at Aurora Biosciences/Vertex Pharmaceuticals from 2000-04. Currently, I am the Group Leader for Molecular Biology at Icagen, Inc., and have been at this position for over a year. A copy of my curriculum vitae is attached as Exhibit A.

3. The invention of the above-referenced patent application provides for the first time nucleic acid encoding human CNG3B, a novel beta subunit of a cyclic nucleotide gated cation channel that is specifically expressed in retina and testes.

4. I have read and am familiar with the contents of this patent application. In addition, I have read the Office Action, mailed November 2, 2004, and the final Office Action, mailed May 4, 2005, for the present application. It is my understanding that the Examiner asserts that the present invention is not supported by a specific, substantial, and credible asserted utility or a well established utility as required by the United States patent laws.

5. This declaration is provided to demonstrate that the identification of the coding sequence for human CNG3B has a specific and substantial utility that is credible to one of ordinary skill in the art.

6. With other subunit(s), CNG3B forms a cyclic nucleotide gated cation channel highly expressed in retina and testes. Upon direct binding of cyclic nucleotides such as cAMP and cGMP, the CNG3B cation channels are activated and become highly permeable to cations such as Na^+ and Ca^{2+}. This activation leads to cell membrane depolarization and increase of Ca^{2+} concentration within the cell. Since the CNG3B channels are capable of modulating cell membrane potential and cytoplasmic Ca^{2+} concentration, which, as a second messenger,

participates in the regulation of signal transduction in relevant tissues, one of skill in the art would reasonably believe that the CNG3B channels are involved in modulating cellular excitability and therefore biological functions in these tissues. Because of the tissue-specific expression of CNG3B in retina and testes, an artisan would also reasonably believe that these CNG3B channels can serve as therapeutic targets for treatment of conditions related to aberrant cell excitability in the retina or testes, *e.g.*, visual disorders or male fertility disorders. The identification of human CNG3B gene therefore has a substantial utility, or a "real world" use, since this discovery makes possible the routine identification of activators and inhibitors of the CNG3B channels, which may be used as therapeutic agents for treating conditions caused by or related to abnormalities in vision or male fertility. This utility relies on the expression of CNG3B channels in the retina or testes and their involvement in the regulation of signal transduction in these tissues. These are specific features of the CNG3B cation channels and not a broad class of ion channels. The present invention thus has a specific utility.

7. The present invention not only provides nucleic acids encoding human CNG3B, but also teaches methods for detecting the activity of the CNG3B channels (*see, e.g.*, page 42, line 23, to page 46, line 2, of the specification) and methods for identifying modulators of the ion channels (*see, e.g.*, page 46, line 5, to page 50, line 19). Upon reading this disclosure, a skilled artisan would be able to readily screen candidate compounds and identify activators or inhibitors of a CNG3B channel, without the need to carry out extensive additional research. The present invention therefore has a real-world use.

8. There are known instances where modulation of an ion channel is useful for treating a specific disease even though the ion channel itself may not directly cause the disease. For example, hypertension can be caused by a variety of illnesses such as renal disease and diabetes. Among the treatment strategies for hypertension is the use of drugs such as calcium channel blockers to relax the vasculature. Relaxing the vasculature to reduce blood pressure is useful and effective, even if the original cause of the hypertension is not directly related to vascular tone. Similarly, it is perfectly reasonable to expect that the targeting of a CNG3B channel, a cyclic nucleotide gated cation channel that is highly expressed in the retina

and testes and is believed to play a role in regulating the biological functions of these tissues, is an appropriate strategy for treating vision disorders or male fertility disorders, whether or not such abnormality is directly caused by altered CNG3B channel activity. In other words, the use of CNG3B as a therapeutic target for treating these disorders is an effective approach whether or not other ion channels may be relevant to the disorders. Thus, the asserted utility of the CNG3B potassium channel of the present application is reasonable and therefore credible to an ordinarily skilled artisan.

9. In summary, it is my scientific opinion that one of skill in the art, at the time the application was filed, would believe the physiological role human CNG3B plays in the modulation of light sensory and sperm motility, and would recognize the specific and real-world utility of the CNG3B encoding nucleic acids of the present invention.

Date: October 4, 2005 By: Ken McCormack

Ken McCormack, Ph.D.

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Industrial Experience

ICAgen Inc. **Group Leader**
6/01/04-present
Team leader for the molecular biology group. Responsibilities include generation of molecular reagents including cDNAs, cell lines, etc. for ion channel drug discovery efforts and evaluation of new targets through RNA expression and target validation strategies including molecular (e.g., siRNA) and pharmacological approaches.

Vertex/Aurora Biosciences, San Diego CA **Principal Scientist**
6/15/2000-5/15/04
Vertex: Ligand and voltage-gated ion channel drug discovery project development. Evaluate, present and coordinate early-stage discovery efforts including target selection. Initiated discovery program for gene family with inflammatory and neuropathic pain indications. Biology team leader/coordinator for early-stage discovery effort (target/assay/HTS/hit validation/med chem support/secondary assay development) targeting neuropathic pain. Head of molecular biology for ion channel group. Provide primary scientific support for several business development efforts.

Aurora: Assay development and HTS for ion channel targets and transporters using fluorescent Ca++ or voltage-dependent dyes or halide-sensitive YFP (1). HTS and UHTSS screening and hit validation. Project leader and liaison for several external collaborative projects. Profiling of endogenous targets in primary cells; generation of immortalized primary cells including neurons.

Deltagen Proteomics/Arcaris Inc., Salt Lake UT **Group Leader**
8/97-5/2000
Oncogenic assay development; immortalization of human primary cells and tumor formation in nude mice with limited sets of oncogenes. Utilization of yeast two-hybrid (Y2H) peptide-binders (to HPV oncogenes) for disruption of protein-protein interactions and development of peptide-target small molecule displacement screening. Received phase I SBIR for screening peptide-inhibitors of HPV E6 and E7 proteins.

Established in-house mammalian cell culture, cDNA libraries and expression systems (retroviral). Design and development of large-scale phenotypic selections (cell cycle arrest, growth factor dependence, apoptosis) and screening of peptide and cDNA expression libraries. Generation of neuronal cAMP-responsive GFP transcriptional reporter cell lines for identification of CRE-regulatory "perturbagens". Responsible for project coordination with academic collaborators (NIH grant).

Academic Research

NIH Postdoctoral Research Fellow **UW Madison**
2/95-7/97
Functional characterization of two distinct K+ channel associated β subunit genes; generation of null-mutant mice for (Kv β1 and Kv β2) and a "knock-in" point mutation of Kv β2 (2). Gene mapping/cloning,

vector construction, ES cell culture, mouse breeding, phenotyping and development of PCR-based genotyping. GST-fusion purification of Kv β proteins.

HFSP Postdoctoral Fellow **Max-Planck-Institute, Goettingen, Germany**
12/92-1/95
Cloning and characterization of the human Kv β1 and Kv β2 genes, including the first functional expression of the major Kv1 family β subunit, Kv β2 (5), chromosomal mapping (4), analyses of splice products, structural modeling based on "data-mining" and limited homologies with NAD(P)H-dependent oxidoreductases (6) (subsequently verified by X-ray crystallographic studies). Pharmacological, molecular, electrophysiological and kinetic modeling analyses of voltage-gated K+ channel (α subunit) conformational activation. Mechanistic characterization of state-dependent drug-channel interaction using single-channel, gating current and whole cell K+ conductance properties in conjunction with mutagenized differentially-4-AP-sensitive channel constructs (7).

NIH Postdoctoral Assistant **Yale University, New Haven, CT**
4/91-10/92
Site-directed mutagenesis, electrophysiological analyses and the first quantification of the voltage-dependent conformational changes of the integral membrane Shaker K+ channel proteins. Analyses of voltage-dependence in gating-mutant channels and multisubunit constructs (8-10).

Education:

1991 Ph.D.,	**California Institute of Technology**	***Molecular/Neurobiology***
1985 B.S.	**UC Santa Cruz**	***Neurobiology***

PhD student **CalTech, Pasadena, CA**
1985-1991
Site-directed mutagenesis and initial electrophysiological analyses of "leucine zipper" motif gating-mutants in Shaker K+ channels. Utilization of gating-mutants and distinct Shaker splice products to determine multimeric nature of K+ channels. Chromosomal walking, library screening to determine unique splice products (11-13).

Bachelor of Science **UC Santa Cruz, CA**
1983-1985
Electrophysiological and pharmacological characterization of muscarinic response involved in a molluscan behavioral response (14).

Awards, Fellowships and Memberships

Medicinal Chemistry series UCSD Extension 6/2002
SBIR National Cancer Institute, Arcaris/Deltagen Proteomics 4/2000
NIH Postdoctoral Fellowship National Institute of Health, UW Madison 95-97
Foreign Postdoctoral Fellow Max Planck Society, MPI fur experimentelle Medizin 94-95
Postdoctoral Fellow Human Frontiers Science Program, MPI fur biophysikalische Chemie 92-93
Member Society for Neuroscience 1992- present

Technical Expertise

Including but not limited to:

Molecular Biology; generation of genomic and cDNA libraries, RNA isolation, cDNA synthesis, library screening, RT-PCR, Northern blots, site-directed PCR and cassette mutagenesis, quantitative PCR coupled

with FACS and phenotypic enrichment cycling, isolation of novel cDNAs from degenerate PCR, generation of transcriptionally active reporters.

Cell Biology and Biochemistry; Assay development (fluorescent optical readout or phenotypic - cell cycle arrest, apoptosis, etc.), drug discovery HTS and med chem support, pharmacological characterization of ion channels and GCPRs, cell culture including primary and ES cells, transfection and retroviral transduction, immortalization of human primary cells, yeast two hybrid (Y2H) screening, Western blotting, immunofluorescence, monoclonal antibody purification, affinity, DEAE, size-exclusion and FPLC chromatography, protein expression/isolation from *E. Coli*, *Xenopus* oocytes and mammalian tissue.

Biophysical & Computational; patch (including single-channel and gating current recordings) and two-electrode recordings, FACS sorting and analysis, bioinformatic "data-mining", structural and kinetic modeling.

Publications

1. McCormack, K., Heim, R., Raj, D., Xu, J. and Gonzalez, J. Mutant yellow fluorescent protein (YFP) (H148Q) as a cell-based probe for HTS of GABA receptors . In preparation. (Neuroscience 2001 abstract #911.11)

2. McCormack K, Connor JX, Zhou L, Ho LL, Ganetzky B, Chiu SY, Messing.A.. Genetic analysis of the mammalian K+ channel β subunit Kv β2 (KCNAB2). **J Biol Chem.** 2002 277(15):13219-28.

3. McCormack T, McCormack K, Nadal MS, Vieira E, Ozaita A, Rudy B. (1999) The effects of Shaker beta-subunits on the human lymphocyte K+ channel Kv1.3. **J Biol Chem**, 274(29):20123-6.

4. Schultz D, Litt M, Smith L, Thayer M, McCormack K. (1996). Localization of two potassium channel beta subunit genes, KCNA1B and KCNA2B. **Genomics** 31(3):389-91.

5. McCormack K, McCormack T, Tanouye M, Rudy B, Stuhmer W. (1995). Alternative splicing of the human Shaker K+ channel beta 1 gene and functional expression of the beta 2 gene product. **FEBS Lett.** 370(1-2):32-6.

6. McCormack, T. and McCormack K. (1994). Shaker K+ channel beta subunits belong to an NAD(P)H-dependent oxidoreductase superfamily. **Cell** 79(7):1133-5.

7. McCormack K, Joiner WJ, Heinemann SH. (1994). A characterization of the activating structural rearrangements in voltage-dependent Shaker K+ channels. **Neuron** 12(2):301-15.

8. McCormack K, Lin L, Sigworth FJ. (1993). Substitution of a hydrophobic residue alters the conformational stability of Shaker K+ channels during gating and assembly. **Biophys J.** 65(4):1740-8.

9. Schoppa NE, McCormack K, Tanouye MA, Sigworth FJ. (1992). The size of gating charge in wild-type and mutant Shaker potassium channels. **Science** 255(5052):1712-5.

10. McCormack K, Lin L, Iverson LE, Tanouye MA, Sigworth FJ. (1992). Tandem linkage of Shaker K+ channel subunits does not ensure the stoichiometry of expressed channels. **Biophys J.** 63(5):1406-11.

11. McCormack K, Tanouye MA, Iverson LE, Lin JW, Ramaswami M, McCormack T, Campanelli JT, Mathew MK, Rudy B. (1991). A role for hydrophobic residues in the voltage-dependent gating of Shaker K+ channels. **Proc Natl Acad Sci U S A** 88(7):2931-5.

12. McCormack K, Lin JW, Iverson, LE, Rudy B. (1990). Shaker K+ channel subunits from heteromultimeric channels with novel functional properties. **Biochem Biophys Res Commun.** 171(3):1361-71.

13. McCormack, K., Campanelli, J.T., Ramaswami, M., Mathew M., Tanouye, M.A. (1989). Leucine zipper motif update. **Nature** 340, 103-104.

14. Morielli AD, Matera EM, Kovac MP, Shrum RG, McCormack KJ, Davis WJ. (1986). Cholinergic suppression: a postsynaptic mechanism of long-term associative learning. **Proc Natl Acad Sci U S A.** 83(12):4556-60.